DIRECT PREPARATIVE METHODS FOR INTERMEDIATES IN THE SYNTHESIS OF SUBSTITUTED 4-HALOQUINOLINES

BY

ROBERT ELLERY JONES

A.B., Cornell College, 1942
M.S., University of Illinois, 1943

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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I. Introduction

The synthesis of several important drugs with antimalarial activity is accomplished through reaction of 4-diethylamino-2-aminopentane with suitably substituted 4-haloquinolines.

Of the several procedures which have been used for introduction of a halogen atom into the four position of the quinoline nucleus, that involving replacement of a 4-hydroxyl group by halogen has been most successful. Almost without exception, 4-hydroxyquinolines must be prepared by use of reactions involving ring closure. The ethyl esters of several β-anilino-substituted acrylic acids have been found[1] to undergo thermal loss of a molecule of ethyl alcohol yielding 4-hydroxyquinoline derivatives.

Preparation of substituted ethyl β-(anilino)acrylates generally has been a tedious two-step process. It therefore seemed desirable to study direct synthetic methods which would proceed in high yield to give the desired compounds. It was also necessary to give some consideration to the mechanisms of the various reactions.

Discussion

A convenient synthesis of 4,7-dichloroquinoline, developed by Price and Roberts,[2] consists of saponification of 3-carbethoxy-4-hydroxy-7-chloroquinoline, thermal decarboxylation of the acid and replacement of the 4-hydroxyl group with chlorine. The 3-carbethoxy-4-hydroxy-7-chloroquinoline is prepared by reaction of *m*-chloroaniline with ethoxymethylenemalonic ester and subsequent thermal cyclization of the ethyl α-carbethoxy-β-(*m*-chloroanilino)acrylate through elim-

ination of ethyl alcohol. During the preparation of ethoxymethylenemalonic ester according to the method of Claisen,[3] considerable loss in yield is experienced; possible means of avoiding this particular step in the synthesis were investigated.

The preparation of numerous β-anilinoacrylates is reported by Dains[4] through reaction of diphenylformamidine with active methylene reagents such as malonic ester, acetoacetic ester and cyanoacetic ester. This reaction probably proceeds through addition of the active methylene reagent to the diarylformamidine[4] and subsequent elimination of a molecule of aniline to form an α-substituted-β-anilinoacrylate. The mole of free aniline produced in this reaction proves very troublesome. In the reaction with malonic ester, the *m*-chloroaniline reacts with the ethyl α-carbethoxy-β-(*m*-chloroanilino)acrylate to form the undesired ethyl α-*m*-chlorocarbanilido-β-(*m*-chloroanilino)acrylate. Application of the reaction to di-(*m*-chloroanilino)formamidine and cyanoacetic ester yields α-cyano-β-(*m*-chloroanilino)acrylate but the mole of free *m*-chloroaniline makes recovery of the product in high yield extremely difficult.

The most convenient preparation of the dairylformamidines is that of Claisen,[3] consisting of reaction of two moles of the aniline with one of ethyl orthoformate. Experimental conditions for this reaction as well as those for the subsequent reaction of the amidine with an active methylene reagent involve only heating of the components at approximately 150°.

A three-component mixture of equimolar amounts of *m*-chloroaniline, ethyl orthoformate and ethyl cyanoacetate was heated at 160° and the volume of alcohol which distilled from the mixture was measured. In a short time, three moles of alcohol had been collected, and it was found that a quantitative yield of ethyl α-cyano-β-(*m*-chloroaniline)-acrylate could be isolated from the reaction mixture. This reaction represents a simple, one-step preparation of an

α-substituted-β-(*m*-chloroanilino)acrylate which may proceed by the intermediate formation of either or both the dairylamidine or the ethoxymethylene derivative of the active methylene reagent. That neither route is exclusive was shown by successful application of the reaction to N-methylaniline (preventing formation of an amidine) and to benzylmalonic ester (preventing formation of an ethoxymethylene derivative).

In surveying the generality of the reaction, variation of the aromatic amine component was found to have little effect upon the yield, aniline, *p*-anisidine, *m*-chloroaniline, N-methylaniline and *m*-trifluoromethylaniline all giving high yields of the expected acrylates. The active methylene reagents submitted to the reaction were malonic ester, acetoacetic ester, cyanoacetic ester, ethyl phenylacetate, acetylacetone, ethyl acetonedicarboxylate and benzylmalonic ester. In each of these reactions the yields of acrylate appeared to be proportional to the activity of the methylene group involved.

BIBLIOGRAPHY

1. Conrad and Limpach, Ber., **20,** 944 (1887).
2. Price and Roberts, Private Communication.
3. Claisen, Ann., **297,** 33 (1897).
4. Dains, Ber., **35,** 2496.
5. Claisen, Ann., **287,** 366 (1893).

VITA

The author was born near Morrison, Illinois, on November 23, 1920. He graduated from the Morrison High School in May, 1938, and matriculated at Cornell College, Mount Vernon, Iowa, in September of the same year. He was granted the degree of Bachelor of Arts in May, 1942, and in the fall of that year entered the Graduate School of the University of Illinois. Until May, 1944, the author held a teaching assistantship and since that time he has been employed as a Special Research Assistant under Contract O. E. M. 321 in the laboratories of the University of Illinois.

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